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Myocardial scintigraphy using a fatty acid analogue detects coronary artery disease in hemodialysis patients

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Myocardial scintigraphy using a fatty acid analogue detects coronary artery disease in hemodialysis patients.

Background. Coronary artery disease contributes significantly to mortality in end-stage renal disease (ESRD) patients. Single-photon emission computed tomography (SPECT) using an iodinated fatty acid analogue, iodine-123®-methyl iodophenylpentadecanoic acid (^{123}I-BMIPP), can assess fatty acid metabolism in the myocardium. We investigated the ability of ^{123}I-BMIPP SPECT to detect coronary artery disease in hemodialysis patients compared with ^{201}thallium chloride (^{201}Tl) SPECT.

Methods. We prospectively studied 130 ESRD patients undergoing hemodialysis for a mean of 88.6 months (male/female, 77/53; mean age, 63.8 years). Dual SPECT using ^{123}I-BMIPP and ^{201}Tl was performed, followed by coronary angiography. SPECT findings were graded in 17 segments on a five-point scale (0, normal uptake; 4, none) and assessed as a summed score.

Results. By coronary angiography, 71.5% of patients (93/130) had significant coronary stenosis ($\geq$75%), and five patients showed coronary spasm without coronary stenosis. When a BMIPP summed score of 6 or more was defined as abnormal, sensitivity, specificity, and accuracy for detecting coronary artery disease by BMIPP SPECT were 98.0%, 65.6%, and 90.0%, respectively; in contrast, these parameters for detecting coronary artery disease by Tl SPECT were 84.7%, 46.9%, and 75.0%, respectively, when a Tl summed score of 1 or more was defined as abnormal. In receiver operating characteristic analysis, the area under the curve was 0.895 in BMIPP and 0.727 in Tl SPECT, respectively.

Conclusion. Resting BMIPP SPECT is superior to Tl SPECT for detecting coronary lesions, and provides safe screening for coronary artery disease among maintenance hemodialysis patients.

Key words: BMIPP, coronary artery disease, end-stage renal disease, hemodialysis, fatty acid.

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Cardiovascular disease is the single best predictor of mortality in patients with end-stage renal disease (ESRD) [1, 2]. Postmortem and coronary angiographic studies have shown that ischemic heart disease from stenosis of coronary arteries is very common in ESRD patients. Prevalence of coronary artery stenosis in ESRD patients varies from 24% in young nondiabetic hemodialysis patients [3] to 85% in elderly diabetic uremic patients [4]. Seventy-three percent of hemodialysis patients were reported to have more than 50% stenosis in one coronary artery [5]. Another study of 67 hemodialysis patients found that 23% of hemodialysis patients demonstrated evidence of silent myocardial ischemia according to ambulatory electrocardiographic monitoring carried out for at least 12 hours [6]. Although the prevalence of coronary artery disease in the dialysis population depends upon the definition used, it appears to be much higher in ESRD patients undergoing hemodialysis than in a non-ESRD population. Coronary angiography, the "gold standard" for diagnosis of coronary disease, is unsuitable for screening for coronary artery disease in hemodialysis patients because vascular complications in coronary artery disease reportedly are nearly 20 times more likely in hemodialysis than in nonhemodialysis patients [abstract; Hajj-Ali R, et al, *Am J Cardiol* 90 (Suppl 6A):168H, 2002]. Effectiveness of combined dipyridamole-exercise ^{201}thallium chloride (^{201}Tl) scintigraphy, combined dipyridamole-exercise stress echocardiography, and dobutamine stress echocardiography in screening for coronary artery disease has been reported in ESRD patients [7, 8, 9]. In practice, however, many patients apparently cannot perform these stress tests properly. Exercise stress sufficient to produce evaluable results may be impossible to attain in some cases because exercise tolerance generally is reduced in hemodialysis patients. Additionally, administration of drugs that influence cardiovascular function may elicit extreme changes in blood pressure or heart rate in hemodialysis patients since their autonomic function

Table 1. Characteristics of the 130 subjects

Male gender %	77 (59.2%)
Age *years*	63.8 ± 10.4
Hemodialysis duration *months*	88.6 ± 89.0
Presence of diabetes mellitus %	61 (46.9%)
Serum hemoglobin A_{1c} concentration ($N = 61$) %	6.1 ± 1.2
Hematocrit %	32.3 ± 2.8
Serum hemoglobin *g/L*	105 ± 9
Serum albumin *g/L*	39.7 ± 4.5
Serum total cholesterol *mmol/L*	4.1 ± 0.3
Systolic blood pressure before hemodialysis *mm Hg*	146 ± 16
Diastolic blood pressure before hemodialysis *mm Hg*	73 ± 11
Systolic blood pressure after hemodialysis *mm Hg*	132 ± 19
Diastolic blood pressure after hemodialysis *mm Hg*	64 ± 10
Cardiothoracic ratio %	52.0 ± 5.1
Left ventricular internal end-diastolic dimension *mm*	50.8 ± 7.3
Left ventricular internal end-systolic dimension *mm*	34.2 ± 7.9
Left ventricular fractional shortening %	33.3 ± 9.7
Left ventricular ejection fraction %	60.6 ± 13.7
Interventricular septal wall thickness *mm*	11.7 ± 3.2
Left ventricular posterior wall thickness *mm*	9.3 ± 2.1

in hemodialysis patients often is impaired. Therefore, a test is needed that requires neither exercise nor drug administration to screen for coronary artery disease in hemodialysis patients. Over 70% of the energy required by the normal myocardium under aerobic conditions derives from metabolism of free fatty acids (FFA) [10]. Under hypoxic or ischemic conditions, fatty acid metabolism is believed to be suppressed and replaced by glucose metabolism, which requires less oxygen consumption [11]. Iodine-123®-methyl iodophenyl-pentadecanoic acid (^{123}I-BMIPP) is a branched FFA analogue characterized by resistance to β-oxidation. Recent studies indicate possible effectiveness of single-photon emission computed tomography (SPECT) using ^{123}I-BMIPP as a tracer in diagnosis of organic coronary lesions, unstable angina pectoris, or coronary spasm without exercise or drugs [12–22]. In the present study, we investigated whether ^{123}I-BMIPP SPECT could be useful in screening for coronary artery disease in ESRD patients undergoing maintenance hemodialysis. This modality was compared with ^{201}Tl SPECT, which has been used for evaluating the coronary circulation.

METHODS

Patients

We prospectively enrolled 130 ESRD patients undergoing maintenance hemodialysis for more than 3 months at Toujinkai Hospital (77 male and 53 female; mean age, 63.8 ± 10.4 years) (Table 1). Patients diagnosed with acute or old myocardial infarction, unstable angina pectoris, idiopathic hypertrophic or dilated cardiomyopathy, or congestive heart failure (New York Heart Association grades III to IV) were excluded. Of 130 subjects, 61 had diabetes mellitus (46.9%), and 23 of 61 diabetic patients had been receiving insulin therapy. Blood pressure was measured hourly during dialysis using a mercury sphygmomanometer; for study purposes it was determined as the mean of the measurements obtained at eight different midweek hemodialysis sessions before examination by myocardial scintigraphy. Hemodialysis was performed three times weekly using a dialysate containing Na^+ (140 mEq/L), K^+ (2.0 mEq/L), Cl^- (110 mEq/L), Ca^{2+} (3.0 mEq/L), Mg^{2+} (1.0 mEq/L), HCO^{3-} (30 mEq/L), and CH_3COO^- (10 to 15 mEq/L). Membranes used in the dialyzer were either cellulose triacetate (FB-190F) (Nipro, Tokyo, Japan), surface modified regenerated cellulose (AMBC-20X) (Asahi Medical, Tokyo, Japan), polymethyl methacrylate (FB-2.1F) (Toray Medical, Tokyo, Japan) or polysulfone (PS-1.9UW) (Kawasumi Laboratory, Tokyo, Japan). Dialysis filter surface areas were 1.8 to 2.1 m^2. The Ethical Committee for Human Research of Toujinkai Hospital approved this study, and all patients provided informed consent for participation.

Radionuclide imaging

All patients underwent resting ^{123}I-BMIPP and ^{201}Tl scintigraphy under pain-free conditions after fasting for over 6 hours. Each dose of 111 MBq of ^{123}I-BMIPP (Nihon Medi-Physics, Tokyo, Japan) and ^{201}Tl (Nihon Medi-Physics) was injected intravenously with patients seated. Fifteen minutes after the injection, data for SPECT were acquired from a 64 × 64 matrix in 32 directions, at 6° intervals from the 45° right anterior oblique position to the 45° left posterior oblique position, for 30 seconds per direction, using a commercially available gamma camera (Starcam 4000i) (GE Medical Systems, Waukesha, WI, USA) equipped with a low-energy, all-purpose collimator. The energy discrimination of ^{123}I-BMIPP was centered at 159 keV with a 20% window, and that of ^{201}Tl was centered at 90 keV with a 20% window. Data were entered into an online nuclear medicine data processor (IMC12C4-5) (GE Medical Systems). Tomographic images then were constructed with short-axis, horizontal-axis, and vertical-axis sections. The threshold level was 20%, and absorption was not corrected. The ventricular SPECT images were divided into 17 segments for semiquantative analysis according to the standard myocardial segmentation for tomographic imaging of the heart established by the American Heart Association [23]. Radioactivity of each segment was graded visually and assigned a score from 0 to 4 (0, normal uptake; 1, mildly reduced; 2, moderately reduced; 3, severely reduced; and 4, no uptake). The sum of scores by BMIPP or Tl SPECT, including 17 myocardial segments, was designated the BMIPP summed score or the Tl summed score. The same experienced technician performed scintigraphic procedures in all cases, and the same two investigators who had no clinical information about the patients interpreted the images in all cases.

Coronary angiography

All patients underwent coronary angiography within 60 days of BMIPP-Tl dual SPECT in the Department of Interventional Cardiology of the Second Kyoto Red Cross Hospital. Stenoses of coronary vessels were coded according to the criteria of the American Heart Association reporting system. Luminal stenoses with 75%, 90%, 99%, or 100% occlusion were defined as significant lesions, while patients with luminal stenoses of 50% or less were included in the normal coronary group.

Table 2. Results of coronary angiography

Coronary stenosis of 75% or greater	93/130 (71.5%)
Right coronary artery	51/130 (39.2%)
Left anterior descending artery	61/130 (46.9%)
Left circumflex artery	52/130 (40.0%)
Left main trunk	6/130 (4.6%)
Single-vessel disease	41/130 (31.5%)
Double-vessel disease	28/130 (21.5%)
Triple-vessel disease	18/130 (13.8%)
Left main trunk	6/130 (4.6%)
Coronary spasm	5/130 (3.8%)

Echocardiographic measurements

A two-dimensionally guided M-mode echocardiogram was obtained for each patient using a single ultrasonographic recorder (UF-8800) (Fukuda Denshi, Tokyo, Japan) on a midweek nondialysis day in the week following BMIPP-Tl dual SPECT. Left ventricular dimensions and left ventricular systolic functions such as percent of left ventricular fractional shortening and left ventricular ejection fraction were measured and calculated.

Biochemical and hematologic determinations

Blood samples (5 mL) were obtained just before initiation of the hemodialysis following the SPECT examination, after the patient had been in the supine position for at least 10 minutes. Hematocrit and serum hemoglobin were determined as the mean from four different measurements within a 2-month period, which included the day of the SPECT examination. Serum concentrations of albumin and total cholesterol were determined as the mean from four different measurements within a 4-month period.

Statistical analysis

Data are expressed as the mean ± SD, and differences between groups were evaluated by one-way analysis of variance (ANOVA), followed by application of Duncan's new multiple-range test. A value of $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Coronary angiography findings

Table 2 summarizes the coronary angiography results in all patients enrolled in this study. Significant coronary stenoses of 75% or more were found in 93 of 130 patients (71.5%); six of these 93 patients had stenosis of the left main trunk. Existence of coronary spasm was ascertained by an ergonovine test in five patients without significant coronary stenosis. Of the 98 patients who had coronary artery disease, including those with coronary spasm, 79 had not noted chest pain or discomfort (80.6%). Prevalences of silent myocardial ischemia were 80.0% in diabetic patients (40/50) and 81.3% (39/48) in nondiabetic patients. Of 93 patients with coronary artery stenosis, percutaneous coronary intervention was performed in 63, and coronary artery bypass grafting was carried out in nine. Age, Tl summed score, and BMIPP summed score were higher in patients with coronary artery disease than in those without (Table 3). Gender, dialysis duration, presence of diabetes mellitus, hematocrit, serum concentrations of hemoglobin, albumin, total cholesterol, blood pressure, cardiothoracic ratio, and echocardiographic parameters such as left ventricular dimensions, left ventricular systolic function, or left ventricular wall thickness did not differ between patients with and without coronary artery disease.

In nondiabetic patients, significant coronary stenosis was found in 44/69 patients (63.8%) as follows: right coronary artery, 27/44 (61.4%); left anterior descending, 25/44 (56.8%); left circumflex, 23/44 (52.3%); and left main trunk, 2/44 (4.5%). Single-vessel disease was present in 21/44 (47.7%); double-vessel disease, 12/44 (27.3%); and triple-vessel disease, 9/44 (20.5%). In diabetic patients, significant coronary stenosis was recognized in 49/61 patients (80.3%) as follows: right coronary artery, 24/49 (49.0%); left anterior descending, 36/49 (73.5%); left circumflex, 29/49 (59.2%); and left main trunk, 4/49 (8.2%). Single-vessel disease was present in 20/49 (40.8%); double-vessel disease, 16/49 (32.7%); and triple-vessel disease, 9/49 (18.4%). The prevalence of left anterior descending lesions was higher in diabetic than in nondiabetic patients ($P < 0.01$).

SPECT summed score and coronary stenosis

Figures 1 and 2 show three illustrative cases with significant coronary stenosis and differences in SPECT imaging between BMIPP and Tl. The mean BMIPP summed score was higher in patients with 75% coronary stenosis (16.74 ± 7.41, $N = 19$) or 90% or greater coronary stenosis (22.39 ± 10.42, $N = 74$) than in those with normal coronary arteries (6.19 ± 9.07, $N = 32$). In contrast, the mean Tl summed score was higher in patients with 90% or greater coronary stenosis (9.12 ± 6.99, $N = 74$) than in those with 75% coronary stenosis (4.26 ± 4.48, $N = 19$) or normal coronary arteries (2.59 ± 3.08, $N = 32$), but did

Table 3. Differences in clinical and single photon emission computed tomography (SPECT) variables between patients with or without coronary artery disease (CAD)

	CAD(+) ($N = 98$)	CAD(−) ($N = 32$)	*P* value
Male gender %	61 (62.2%)	16 (50.0%)	0.301
Age *years*	65.2 ± 9.3	59.6 ± 12.4	0.008
Hemodialysis duration *months*	85.7 ± 82.5	96.9 ± 107.5	0.540
Presence of diabetes mellitus %	50 (51.0%)	11 (34.4%)	0.109
Serum hemoglobin A1c concentration %	6.1 ± 1.1	5.9 ± 1.3	0.677
Systolic blood pressure before hemodialysis *mm Hg*	146 ± 16	145 ± 17	0.670
Diastolic blood pressure before hemodialysis *mm Hg*	73 ± 12	76 ± 10	0.166
Systolic blood pressure after hemodialysis *mm Hg*	133 ± 18	128 ± 20	0.134
Diastolic blood pressure after hemodialysis *mm Hg*	63 ± 10	65 ± 9	0.361
Cardiothoracic ratio %	52.3 ± 5.0	51.1 ± 5.2	0.228
Hematocrit %	32.2 ± 2.9	32.4 ± 3.2	0.869
Serum hemoglobin *g/L*	105 ± 8	104 ± 9	0.553
Serum albumin *g/L*	39.5 ± 3.7	40.1 ± 4.8	0.462
Serum total cholesterol *mmol/L*	4.1 ± 0.4	4.0 ± 0.3	0.286
LVIDd *mm*	51.2 ± 7.3	49.5 ± 7.1	0.228
LVIDs *mm*	34.8 ± 8.4	32.5 ± 5.7	0.154
LVFS %	32.7 ± 9.9	35.1 ± 8.8	0.216
LVEF %	59.7 ± 14.4	63.2 ± 11.0	0.200
IVST *mm*	11.8 ± 3.4	11.6 ± 2.7	0.817
PWT *mm*	9.3 ± 2.2	9.5 ± 1.7	0.646
T1 summed score	7.9 ± 6.8	2.6 ± 3.1	<0.001
BMIPP summed score	21.2 ± 10.0	6.2 ± 9.1	<0.001

Coronary artery disease included both coronary artery stenosis and spasm. Abbreviations are: LVIDd, left ventricular internal end-diastolic dimension; LVIDs, left ventricular internal end-systolic dimension; LVFS, left ventricular fractional shortening; LVEF, left ventricular ejection fraction; IVST, interventricular septal wall thickness; PWT, left ventricular posterior wall thickness.

not differ between the 75% coronary stenosis and the normal coronary groups (Fig. 3). In BMIPP and Tl SPECT, the mean summed score was higher in patients with 90% or greater coronary stenosis than in those with normal coronary arteries, irrespective of whether this stenosis involved the right coronary artery, left anterior descending, or left circumflex. In BMIPP SPECT, the mean summed score of patients with 75% stenosis was higher when this stenosis involved the left anterior descending, and tended to be higher when the right coronary artery was involved, than the mean summed score of the normal coronary group. In contrast, the mean summed score in Tl SPECT did not differ between the 75% coronary stenosis and normal coronary groups irrespective of which coronary artery was involved.

SPECT summed score and number of coronary vessels with significant stenosis

The mean BMIPP summed score was higher in patients with single-vessel (19.34 ± 10.07, $N = 41$), double-vessel (20.75 ± 9.59, $N = 28$), or triple-vessel coronary disease (23.11 ± 10.19, $N = 18$) or in the left main trunk stenosis group (30.83 ± 8.13, $N = 6$), than in the normal coronary group (6.19 ± 9.07, $N = 32$). On the other hand, the mean Tl summed score was higher in patients with double-vessel coronary disease (7.36 ± 6.07, $N = 28$), triple-vessel disease (10.33 ± 7.78, $N = 18$), or left main trunk stenosis (16.17 ± 5.34, $N = 6$) than in those with normal coronary arteries, but did not differ between patients with single-vessel disease (6.39 ± 6.15, $N = 41$) and those with normal coronary arteries (Fig. 3).

Diagnostic potential of BMIPP-Tl SPECT

Receiver operating characteristic curves indicated that ability to diagnose coronary artery disease in hemodialysis patients was higher for BMIPP SPECT than for Tl SPECT (Fig. 4). When a BMIPP summed score of 6 or more was defined as abnormal, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of detecting coronary artery disese by BMIPP SPECT were 98.0%, 65.6%, 89.7%, 91.3%, and 90.0%, respectively. In contrast, these parameters for detecting coronary artery disease by Tl SPECT were 84.7%, 46.9%, 83.0%, 50.0%, and 75.0%, respectively, when a Tl summed score of 1 or more was defined as abnormal.

Left ventricular function and BMIPP summed score in the normal coronary group

When a BMIPP summed score of 6 or more was defined as abnormal, significant differences were recognized between normal BMIPP ($N = 21$) and abnormal BMIPP ($N = 11$) groups in percent of left ventricular fractional shortening [37.5 ± 9.2% ($N = 21$) vs. 30.5 ± 5.7% ($N = 11$), $P < 0.05$] and left ventricular ejection fraction [66.2 ± 11.1% ($N = 21$) vs. 57.6 ± 8.4% ($N = 11$), $P < 0.05$]. Age, gender, presence of diabetes mellitus, serum hemoglobin A_{1c} concentration, hematocrit, serum concentrations of hemoglobin, albumin, total cholesterol, cardiothoracic ratio, blood pressure before or after dialysis, left ventricular dimension, and left ventricular wall thickness did not differ between the two groups.

Left ventricular wall thickness and BMIPP summed score

No significant correlation was found between interventricular septal wall thickness measured at the left ventricular base and the BMIPP score of the basal anteroseptal segment ($r = 0.069$, $P = 0.433$, $N = 130$) or between left ventricular posterior wall thickness measured at the left ventricular base and the BMIPP score of the basal inferolateral segment ($r = 0.022$, $P = 0.802$, $N = 130$).

DISCUSSION

In the present study, coronary artery disease demonstrated high prevalence of significant coronary artery stenosis (71.5%) in maintenance hemodialysis patients.

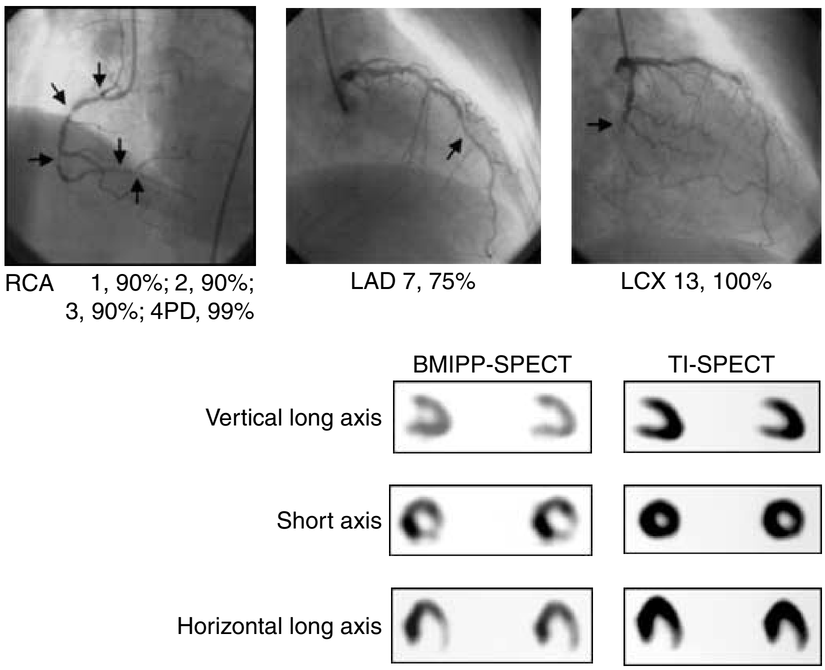

Fig. 1. A hemodialysis patient of 75-year-old woman showing triple-vessel disease by coronary angiography and differences in imaging between BMIPP and Tl singlephoton emission computed tomography (SPECT). Abbreviations are: RCA, right coronary artery, PD, posterior descending branch, LAD, left anterior descending artery; LCX, left circumflex artery.

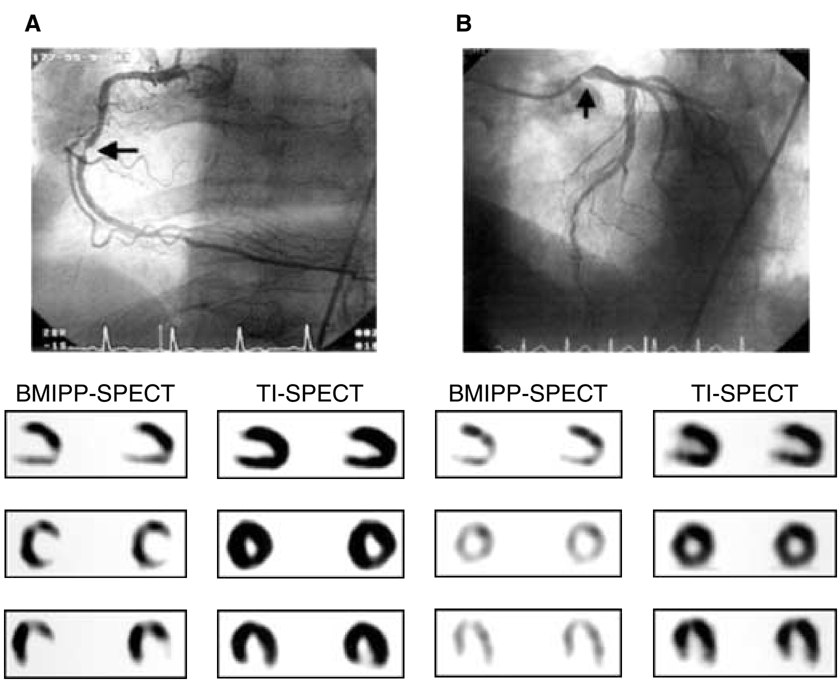

Fig. 2. Two hemodialysis patients showing significant coronary stenosis by coronary angiography and differences in imaging between BMIPP and Tl single-photon emission computed tomography (SPECT). (*A*) A 60-year-old man, 90% stenosis of segment 2 of the right coronary artery. (*B*) A 70-year-old man, 90% stenosis of the left main trunk.

Nearly 80% of these patients with coronary artery disease had no apparent chest pain, independent of the presence of diabetes mellitus. The mean BMIPP summed score was higher in hemodialysis patients not only with 90% or greater but also those with 75% coronary stenosis, than the scores in those with normal coronary arteries. Furthermore, the mean BMIPP summed score was higher in patients with single-vessel disease, as well as those with double- or triple-vessel disease or as left main trunk lesion, than in those with normal coronary arteries. When a BMIPP summed score of 6 or more was defined as abnormal, sensitivity, specificity, and accuracy for detecting coronary artery disease by BMIPP SPECT were 98.0%, 65.6%, and 90.0%, respectively, while these parameters for detecting coronary artery disease by Tl SPECT were 84.7%, 46.9%, and 75.0% when a Tl summed score of 1 or more was defined as abnormal. Based on receiver operating characteristic curve analysis, BMIPP SPECT was superior to Tl SPECT for detecting coronary artery disease in hemodialysis patients.

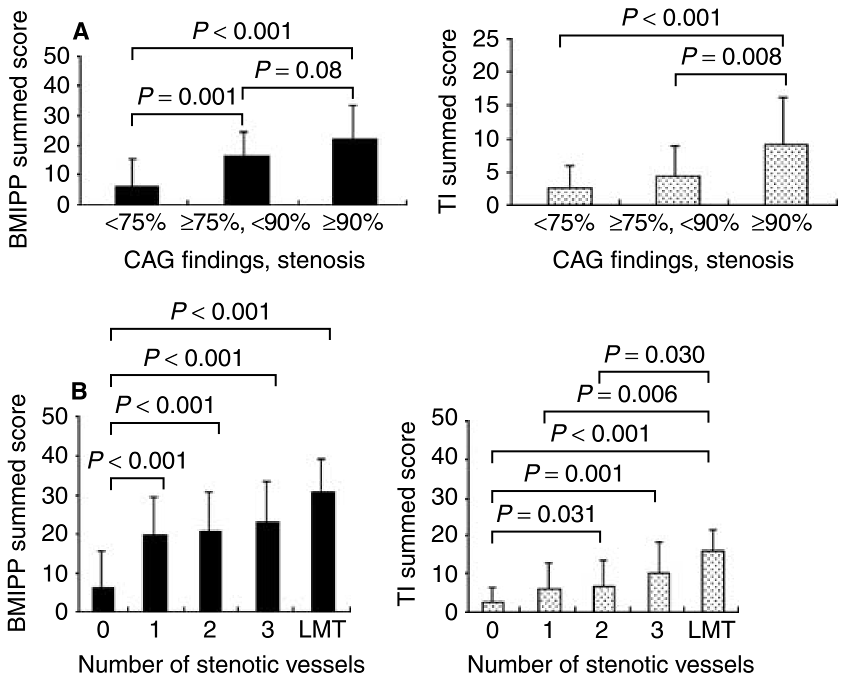

Fig. 3. Relationships of BMIPP and Tl single-photon emission computed tomography (SPECT) to coronary artery disease identified by coronary angiography (CAG). (*A*) BMIPP and Tl SPECT summed scores according to degree of coronary artery stenosis. (*B*) BMIPP and Tl SPECT summed scores according to number of coronary vessels with significant stenosis (75% or more).

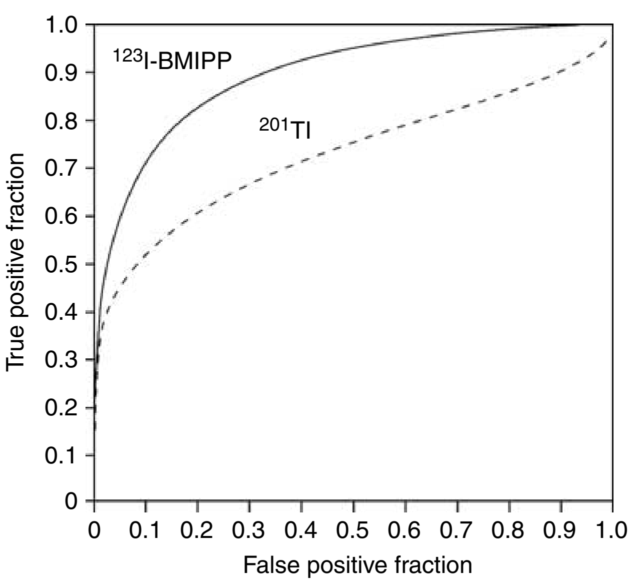

Fig. 4. Receiver operating characteristic (ROC) curves indicating the diagnostic potential for coronary artery disease of ^{123}I-BMIPP and ^{201}Tl single-photon emission computed tomography (SPECT). The area under the curve (AUC) was 0.895 for BMIPP and 0.727 for Tl SPECT, respectively.

The metabolism and kinetics of BMIPP in myocardial cells are determined by the following factors: (*1*) incorporation from the blood into cardiac muscle cells via the CD36-positive FFA binding protein on the myocardial cell membrane; (*2*) the back diffusion from within myocardial cells into the blood that occurs immediately after incorporation (early back diffusion); (*3*) intracardiac concentrations of adenosine triphosphate (ATP), which is required for acylation of BMIPP to acetyl-BMIPP; (*4*) accumulation in the lipid pool (about 70%); (*5*) metabolism to ρ-iodophenyl acetic acid via α- or β-oxidation in mitochondria (about 10%); and (*6*) back diffusion from the lipid pool into the blood (late back diffusion). Of these factors, intracardiac ATP and accumulation in the lipid pool are believed to be significantly associated with early cardiac imaging findings by BMIPP SPECT [24–30].

Sensitivity of detection of coronary artery stenosis by BMIPP SPECT has been reported to be higher in unstable angina (61% to 74%) [19, 21, 22], than in stable angina (31.7% to 50.0%) [18, 21]. The overall detection rate of coronary artery lesions obtained in this study was higher than those reported in either unstable angina or stable angina without ESRD. The high detection rate of coronary artery disease by BMIPP SPECT in hemodialysis patients may be partially explained by structural and metabolic myocardial abnormalities that are peculiar to hemodialysis patients.

In experimental models of renal failure and in uremic patients, intramyocardial arteriolar wall thickening is consistently observed independently of blood pressure [31, 32]. Thickening of the vascular wall includes distinct hypertrophy of vascular wall cells as well as a slight increase in the number of cells [33]. Parathyroid hormone or endothelin may be involved in this arteriolar thickening in hemodialysis patients [34, 35]. In addition, reduction of capillary density in the myocardium has been reported in animal models of renal failure and in uremic patients [31, 36, 37]. Furthermore, an autopsy study reported that interstitial fibrosis in the myocardium was more severe in ESRD patients than in patients with primary hypertension and diabetes mellitus [37]. Myocardial fibrosis in hemodialysis patients is not substitution of scar tissue as seen in parenchymal necrosis, but shows a different pattern resulting from primary activation of cardiac interstitial fibroblasts. Intramyocardial arteriolar thickening is likely to interfere with vasodilation. Reduction of capillary density and myocardial fibrosis increase intercapillary diffusion distance, decreasing blood and oxygen supply to cardiomyocytes. All of these myocardial abnormalities in hemodialysis patients render the myocardium more susceptible to ischemic injury. When coronary artery stenosis or spasm is present, myocardial ischemia is thought to be more severe in hemodialysis patients than in other patients. Myocardial ischemia reduces the myocardial lipid pool by a shift from lipid to glucose metabolism, and also decreases myocardial ATP concentrations, which would inhibit synthesis of acetyl-BMIPP and further decrease accumulation of acetyl-BMIPP to the reduced lipid pool. Therefore, when significant coronary stenosis is present, myocardial accumulation of ^{123}I-BMIPP appears to decrease more sharply in hemodialysis patients than in nonhemodialysis patients.

A significant drop below 80 mm Hg in mean oxygen tension reportedly occurs during hemodialysis [38, 39]. In addition, blood pressure sometimes reduces to preshorck levels during hemodialysis, in which inhibited sympathetic activity or enhanced nitric oxide production are likely to be involved [40, 41]. Repeated hypoxemia or hypotension during hemodialysis possibly aggravate myocardial ischemia in hemodialysis patients with significant coronary artery stenosis. Although we do not have direct evidence to prove it, repeated dialysis hypoxemia or hypotension may have partially contributed to high detection rate of coronary artery disease by BMIPP SPECT in chronic hemodialysis patients.

Carnitine plays an important role in transport of long-chain FFA from the cytoplasm to the matrix of myocardial and skeletal muscle mitochondria. Maintenance hemodialysis patients are in a state of chronic free carnitine deficiency, because their diets are limited in foods containing carnitine, renal synthesis of carnitine is decreased, and circulating carnitine is removed during hemodialysis [42]. Chronic administration of L-carnitine to hemodialysis patients reportedly did not change accumulation of ^{123}I-BMIPP in the myocardium or left ventricular dimension or function, but it increased the washout rate of ^{123}I-BMIPP [43]. Experimental administration of etomoxir, a carnitine palmotoyltransferase I inhibitor, to dogs did not affect retention of ^{123}I-BMIPP in the heart [32]. Therefore, carnitine deficiency may have some influence on lipid metabolism in myocardial cells, but would not seem likely to significantly alter ^{123}I-BMIPP SPECT imaging in maintenance hemodialysis patients.

Circulating FFA increases during hemodialysis, and plasma FFA concentration is reportedly elevated in uremic patients [44, 45]. Increased circulating FFA may affect the myocardial uptake of BMIPP, because BMIPP is a branched FFA. In an animal experiment of intravenous infusion of triglycerides, the extraction of ^{123}I-BMIPP in canine myocardium decreased, the washout and backdiffusion increased, but the myocardial retention level of ^{123}I-BMIPP remained constant [46]. In a human study, however, myocardial uptake and clearance of ^{123}I-BMIPP had no relation to the levels of blood triglycerides or FFA, and the detection rate of significant coronary artery disease by ^{123}I-BMIPP SPECT did not differ between the groups of patients with or without hyperlipidemia [47]. Thus, it seems to be unlikely that increased circulating FFA affects the detection rate of coronary artery disease by ^{123}I-BMIPP SPECT in chronic hemodialysis patients, although we cannot deny the possibility. Further study is needed to clarify the relationship between increased circulating FFA and BMIPP SPECT in chronic hemodialysis patients.

Mismatch between BMIPP and Tl SPECT was observed in hemodialysis patients with coronary artery disease. This mismatch is usually seen in cases of impaired fatty acid metabolism despite restored coronary perfusion such as stunned myocardium. However, the mechanism causing BMIPP-Tl mismatch in chronic hemodialysis patients with coronary artery disease may be different from that of stunned myocardium. In a study which assessed the relationship between ^{123}I-BMIPP uptake and myocardial fibrosis in chronic hypoperfused human heart, Kudoh et al [48] disclosed that BMIPP-Tl mismatch was found only in ischemic myocardium in which the extent of fibrotic changes was less than 20%. Interstitial fibrosis in the myocardium is generally recognized in ESRD patients [37], as described above. Myocardial fibrotic changes in chronic hemodialysis patients with coronary artery disease are not likely to be severe because left ventricular function was relatively reserved. BMIPP-Tl mismatch in chronic hemodialysis patients without acute myocardial ischemia may indicate changes in fatty acid metabolism of the ischemic myocardium that has mild interstitial fibrosis.

Specificity of BMIPP SPECT for diagnosis of coronary artery disease in hemodialysis patients (65.6%) was considerably lower than sensitivity, and also was lower than specificity in nonhemodialysis patients (80% to 93.8%) according to the previous reports [18, 21]. In the normal coronary artery group, almost one third of patients showed a high BMIPP score of 6 or more. Left ventricular fractional shortening and ejection fraction, which are parameters of left ventricular systolic function and depend largely on myocardial ATP, were less in patients with a higher BMIPP summed score than in those with a lower BMIPP summed score within the normal coronary group. This finding may reflect abnormalities of myocardial microcirculation induced by the structural changes, which are likely to be greater in patients with a higher BMIPP summed score. Further investigation is needed to clarify the mechanism of reduced uptake of BMIPP in hemodialysis patients with normal coronary arteries.

Results of the present study showed that prevalence of silent myocardial ischemia is unexpectedly high in chronic hemodialysis patients. We aimed to exclude the patients with apparent history or echocardiographic findings showing the presence of old myocardial infarction from the subjects. However, as a study limitation, we may have not been able to completely exclude the patients with a small and mild old myocardial infarction induced by silent myocardial ischemia from the study because electrocardiographic abnormalities often are difficult to interpret in hemodialysis patients and echocardiographic findings are sometimes within normal range in a revascularized small old myocardial infarction.

Because all subjects of the present study were outpatients who had been going to hospital regularly, only early image BMIPP and Tl dual SPECT was carried out in the present study. Results of the present study indicate that an early image of BMIPP SPECT is enough for screening of coronary artery disease without spending time. However, it would be meaningful to evaluate the diagnostic value of delayed image as well as early image of BMIPP SPECT for detecting coronary artery disease in hemodialysis patients, because addition of delayed image may improve the diagnostic potential of BMIPP SPECT.

CONCLUSION

Results obtained in this study indicate greater usefulness for resting ^{123}I-BMIPP SPECT in detection of coronary artery disease in chronic hemodialysis patients than for ^{201}Tl SPECT. The high sensitivity and accuracy in detecting coronary artery stenosis demonstrated that resting ^{123}I-BMIPP SPECT appears adequate for screening for coronary artery disease in hemodialysis patients. The number of ESRD patients undergoing maintenance hemodialysis is increasing every year, with the most common underlying disease being diabetes mellitus, where atherosclerosis/arteriosclerosis generally occurs systemically including coronary artery involvement. To decrease risk of future cardiac events such as acute myocardial infarction or congestive heart failure caused by myocardial ischemia in chronic hemodialysis patients, asymptomatic coronary artery disease should be diagnosed as soon as possible, ultimately by coronary angiography, and then treated by percutaneous coronary intervention or coronary artery bypass grafting. We believe that resting ^{123}I-BMIPP SPECT provides sufficient information to determine whether a maintenance hemodialysis patient with no apparent chest pain should undergo coronary angiography.

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